Commission of the European Communities

environment and quality of life

REPORTS of the Scientific Committee on Cosmetology

(fifth series)

Report

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Directorate-General
Environment, Consumer Protection and Nuclear Safety

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FORWARD

The Scientific Committee on Cosmetology was set up by Commission Decision 47/45/EEC on 19 December 1977 (OJ N° L 13 of 17 January 1978, p. 24) in order to provide the Commission with informed opinions on any scientific and technical problems arising in connection with cosmetic products, and in particular on the substances used in their manufacture, on their composition and on the conditions for their use.

The members of the Committee are independent scientists highly qualified in the fields of medicine, toxicology, biology, chemistry or other similar disciplines.

The Committee is serviced by the Directorate-general for the environment, consumer protection and nuclear safety.

This volume contains a collection of the Committee's fifth reports setting out the opinions it delivered on the dates given in the headings.

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(3) Resigned on 18.2.1985
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(5) Resigned on 30.4.1986

REPORT OF THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING THE USE OF N-(HYDROXYMETHYL)-N-(1,3-DIHYDROXYMETHYL-2,5-DIOXO-4-IMIDAZOLIDINYL)-N'-(HYDROXYMETHYL) UREA AS A PRESERVATIVE

(Opinion delivered on 25 March 1985)

TERMS OF REFERENCE OF THE COMMITTEE

To give an opinion on the use of N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl) urea as a preservative at a maximum concentration of 0.5% in the finished cosmetic product.

CONCLUSION

The Committee requests further tests on N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl) urea to examine genotoxic properties and to establish the type of systemic toxicity upon sufficiently high oral exposure, and on the amount of formaldehyde released from this substance. On the basis of the existing data, however, it can approve the provisional use of N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl) urea as a preservative in cosmetics at a maximum concentration of 0.5 % in the finished product.

BACKGROUND

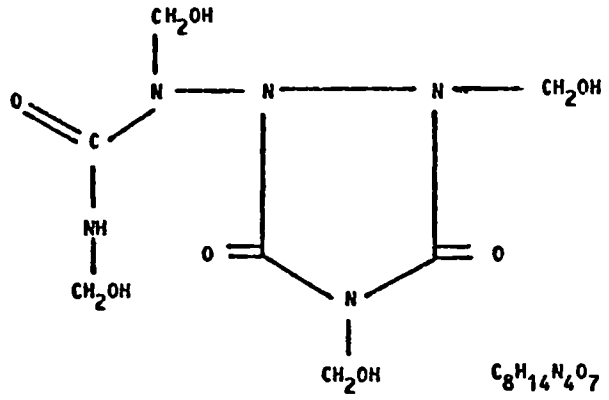
1. Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Council Directive 84/415/EEC, authorizes the placing on the market of cosmetic products containing as a preservative only the substances listed in Annex VI to the said directive, within the limits and concentrations specified therein.

2. The industry has requested that N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl) urea be added to that Annex as a new preservative agent in the cosmetic products and has submitted a scientific dossier in support of its request.

3. The Committee is consequently invited to express an opinion on the use of N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl) urea as a preservative at a maximum concentration of 0.5% in the finished cosmetic product.

DISCUSSION

4. Chemical name : N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'-(hydroxymethyl)-urea



$C_8H_{14}N_4O_7$

MW 278.23

5. Synonyms : Diazolidinylurea, Germal II

6. Soluble in water; insoluble in most organic solvents.

7. This substance is known to release formaldehyde, the maximum amount being 10 %, as determined by a destructive method.

8. Use level up to 0.5%.

9. The oral LD_{50} in rats was 2570 mg/kg.
The dermal LD_{50} in rabbits, when applied undiluted as a powder, was $>$ 2000 mg/kg.

10. Skin irritation tests in rabbits with 0.5 ml of 1.0% and 5.0% solutions in water were negative.

11. An eye irritation test in rabbits with 0.1 ml of 1.0 and 5.0% aqueous solutions did not induce any changes.

12. In a sensitization test in guinea pigs by the Landsteiner-Draize method, the induction treatment consisted of 10 intracutaneous injections of 0.1 ml 0.1% in saline solution. After a 2 weeks rest period, 0.05 ml of a 0.1% solution was given intracutaneously as a challenge. The test was considered negative.

13. In a maximization test in guinea pigs induction was performed with the undiluted substance applied topically and with a 5% solution applied intradermally. The induction areas were pretreated with sodium lauryl sulphate. The response to the challenge treatment, conducted 2 weeks later, suggested the test substance to be a weak sensitizer.

14. Phototoxicity tests in groups of 9-11 human subjects with 0.2 g sunscreen cream or sunscreen lotion containing 0.5% diazolidinyl urea, did not induce signs of phototoxicity, when applied 10 times on a closed patch for 24 hours, followed by UV- or UV-A-irradiation at a distance of 10 cm during 15 minutes. A similar phototoxicity test in 11 subjects with one application of 0.2 g sunscreen lotion containing 0.5% and irradiated with UV-A was likewise negative.

15. A sensitization study in 110 women was conducted with a sunscreen formulation containing 0.25% of the preservative applied with 10 successive patches under semi-occlusion. The challenge patch with the same formulation, after a 2 week rest, resulted in only one dubious, positive reaction.

    No cross-sensitization was observed in 71 patients (who had shown sensitization to various preservatives and other chemicals) upon patch testing with 0.5 and 1.0% Germall II in water and in petrolatum.

16. In several photosensitization tests, groups of 28-30 human subjects were treated with 0.2 g of 0.5% in a sunscreen cream, or in a sunscreen lotion 10 times, each time for 24 hours and each treatment followed by UV-, UV-A, or UV-B-irradiation for 15 minutes. After a 10-18 days rest period, the challenge treatment with an occluded patch for 24 hours followed by UV, UV-A or UV-B-irradiation did not reveal photoallergic properties, although one slight transient reaction was observed.

A skin cleanser with 0.3 % was examined in a prophetic patch test on 104 subjects and in a repeat insult patch test on 52 subjects. No positive reactions were observed.

17. In a 90-day oral rat study the test substance was fed in the diet at levels providing 0, 10, 25 or 100 mg/kg bw. There were no treatment-related changes in growth rate, haematology and clinical chemistry or in the results of the pathological examinations. Therefore, 100 mg/kg was considered to be a no-toxic effect level.

18. The Ames test, which was conducted repeatedly with dose levels up to 800 µl/plate showed signs of a positive response, but the results were inconclusive.

19. The Committee requests further tests to examine genotoxic properties and to establish the type of systemic toxicity upon sufficiently high oral exposure and information on the amount of formaldehyde released from this substance.

20. On the base of the existing data, however, it can approve the provisional use of N-(hydroxymethyl)-N-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-N'- (hydroxymethyl) urea as a preservative in cosmetics at a maximum concentration of 0.5% in the finished product.

21. Information : Colipa dossier, Submission I, January 6, 1983
" II, April 14, 1983
" III, December 12, 1983
" IV, June 3, 1985
" V, June 3, 1985

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING THE USE OF ETIDRONIC ACID AND SALTS THEREOF IN COSMETIC PRODUCTS

(Opinion delivered on 25 June 1985)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion concerning the use of etidronic acid and salts thereof in oral-hygiene products, hair-care products and soaps.

CONCLUSION

The Committee considered that the use of etidronic acid and its salts in mouthwash products, hair-care products and soaps did not constitute a health risk if such use were in accordance with the restrictions and conditions set out in paragraph 2. Only a majority of the members were able to recommend the use of etidronic acid and its salts in toothpastes.

BACKGROUND

1. Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 84/415/EEC, contains no special provisions to govern etidronic acid and salts thereof.

2. One Member State has suggested that the use in cosmetic products of etidronic acid and salts thereof, which are substances which exert a medicinal effect, be made subject to the following conditions and restrictions :

Field of application and/or use	Maximum authorized concentration in the finished product
Toothpastes	0.5%) Expressed as acid
Oral-hygiene products	1.0%)
Hair-care products	1.5%)
Soaps	0.2%)

3. The Committee was therefore requested to express an opinion concerning the use of etidronic acid and salts thereof in cosmetic products in accordance with the proposed conditions.

DISCUSSION

4. Since etidronic acid (HEDP) exerts a marked effect on calcium metabolism, it would be necessary to have precise knowledge of the purity criteria, because the presence of any fluorine of phosporic origin would play an important part in the assimilation and elimination of calcium.

5. HEDP exists as an acid, as a disodium salt and as a dicalcium salt. Most of the toxicity tests were carried out on the disodium salt, but in the acute-toxicity and absorption studies all three forms were tested.

6. The oral LD_{50} results varied between 1 g/kg and 11 g/kg, according to the species of animal and the form tested; the dicalcium salt proved to be the least toxic. When the intraperitoneal route was used in mice, the LD_{50} was 0.285 g/kg with the acid form.

7. Intestinal absorption after oral administration varied between |0.6 and 13.6|, according to the species. The sparingly soluble dicalcium salt was absorbed only at the rate of 0.08% (2% of the absorption rate of the disodium salt). In man, absorption increases in proportion to the dose ingested. Approximately 10% of the absorbed dose was found in the skeleton, the rate of accumulation varying with the age of the animal. HEDP in an untransformed state was excreted in the faeces and the urine.

8. At a low dose, HEDP appeared to encourage assimilation of Ca^{++} in the bones. At a high dose, increased absorption by the intestinal tract accompanied by increased urinary excretion of Ca^{++} resulted in a reduction both of Ca^{++} retention and of bone Ca^{++}. Inhibition of the mineralization of epiphyseal cartilage was observed. It would be advisable to ascertain the borderline between the beneficial and the adverse effects of this substance in the organism.

9. HEDP had a slightly irritant effect on the eyes and skin. It reacted positively to a Magnusson and Kligman maximization test (5/25).

10. In the acute subcutaneous toxicity studies in rats, an adverse influence was observed on the formation of bony tissue at doses of 2 mg/kg b.w./day or more. Administration of 0.2 and 0.4 mg/kg b.w./day caused an increase in hard tissue resulting from reduced absorption without any change in the effect on formation.

11. In acute oral tests in cats and rats, the main effects observed were dose-related renal ones, changes in bony tissue and considerable fluctuations in blood calcium and phosphorus levels. In rats, the no-effect level (NEL) was 100 mg/kg b.w./day.

12. Chronic (two years) oral administration of 0.25-100 and 500 mg/kg b.w./day had no carcinogenic effect in rats. The no-effect level, as regards the blood picture and urine and blood chemistry, appeared to be 25 mg/kg b.w./day. It was noted that the test took no account of the composition of bony tissue.

13. An oral-route reproduction and teratogenicity study on two generations of rats revealed an effect on reproduction when 250 mg/kg b.w. was administered; a reduction in the number of implants and corpora lutea was observed. The no-effect dose was 50 mg/kg b.w.

14. Several oral-route teratogenicity studies in rats and rabbits also showed a reduction in the number of implants and live foetuses and an increase in the number of skeletal abnormalities. The no-effect dose was 50 mg/kg b.w. in both species.

15. The mutagenicity tests on bacteria (salm. typh.) and mammals in vivo (micronucleus - mice) proved negative.

16. In man, clinical studies involving patients with osteoporosis showed that the average absorption was about 10%, of which 20% was excreted in the urine. Doses of 20 mg/kg/day for 6 to 12 days caused an increase in blood calcium and blood phosphorus and a reduction in bony tissue, accompanied by an increase in the excretion of calcium.

17. The no-effect levels determined in different studies, whether acute or chronic, and in reproduction and teratogenicity studies were between 25 and 50 mg/kg b.w. On this basis, applying a safety factor of 100, the acceptable daily intake (A.D.I.) in man was calculated to be between 0.25 and 0.50 mg/kg b.w.

18. The first doses used in therapy were 5 mg/kg and the pharmacological effects in adults were clearly apparent at 20 mg/kg b.w./day. The corresponding dose for children was calculated at 2 mg/kg b.w./day.

19. The Committee considered that the safety margin between the dose for cosmetic use in toothpastes and doses exerting a pharmacological and toxic effect was low, especially in children in whom undesirable reactions might be feared: normal use of a toothpaste containing 0.5% of the substance exposed a 20 kg child who ingested approximately 35% of it to an HEDP dose of some 6 mg, i.e. 0.3 mg/kg b.w./day.

20. The Committee consequently felt able to accept the use of etidronic acid and salts thereof in mouth wash products, hair-care products and soaps under the conditions set out in section 2.
However, only a majority of its members was able to give a favourable opinion on their use in toothpastes.

SUPPLEMENTARY OPINION

on

1,3-DIAMINOBENZENE (m-PHENYLENEDIAMINE)

(Opinion delivered on 7 January 1986)

1. In its opinion delivered on 2 September 1980[1] the Scientific Committee on Cosmetology deemed the use of 1,3-diaminobenzene (m-phenylenediamine) acceptable for use in hair dyes.

2. In application of Article 12 of Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, which allows any Member State to prohibit provisionally the marketing of a cosmetic product in its territory or subject it to special conditions, if it finds on the basis of a "substantiated justification" that this product, although complying with the requirements of the Directive, represents a hazard to health, a Member State prohibited the use of m-phenylenediamine in hair dyes in the light of the findings of recent experiments which indicate that:

   - 1,3-diaminobenzene (m-phenylenediamine) and its oxidation products pass through the skin of rats and are excreted in the urine,
   - the elimination products induce frameshift mutations in microsomal tests on salmonella (AMES test),
   - mutagenic activity is concentrated in two urine fractions,
   - mutagenic activity is higher in the urine of rats treated with the oxidized dye than in that of rats treated solely with m-phenylenediamine.

3. Consequently, the Scientific Committee on Cosmetology reviewed the opinion it delivered on 2 September 1980 in the light of these new findings.

4. It concluded that the experimental conditions of the studies referred to in paragraph 2 did not correspond to the conditions of cosmetic use in the following respects:

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(1) Report EUR 8634

1. The nature of the mixture applied: m-phenylenediamine is never applied on its own or mixed solely with H_2O_2 in the dye mixture; the presence of precursors of the paratype is necessary for coloured pigments to form by oxidative copulation. The molecular size of the pigmented material formed and its relatively high molecular weight are not conducive to percutaneous penetration.

2. The method of application: application for 24 hours on shaved skin and under occlusion is conducive to penetration compared to limited contact with the scalp for 30 minutes, before rinsing.

3. The choice of the rat as the experimental animal, since its skin is much more permeable than the human skin.

5. Consequently, the Scientific Committee on Cosmetology considers that, although these latest studies are interesting from a scientific point of view, they do not adduce any significant arguments which would cause it alter its opinion delivered on 2 September 1980.

FURTHER OPINION CONCERNING THE USE OF 1,1,1-TRICHLOROETHANE IN COSMETIC PRODUCTS

(Opinion expressed on 8 October 1985)

- The Committee has studied the arguments in favour of the safeguard clause that one Member State has applied to the use of 1,1,1-trichloroethane in cosmetic products.

- These arguments lack precision and are not considered convincing because the specific toxicity of 1,1,1-trichloroethane as a function of the dose/effect relationships, has not been clearly established; the effects mentioned namely on the kidneys, liver, heart, etc., have been observed only with very high doses and are reversible, while the inhalation exposure level in cosmetic use is very low (< 50 ppm).

- The Committee considers that it cannot express a final opinion until it receives the results of the National Cancer Institute's carcinogenicity studies; it also considers that, in the absence of further information, this compound constitutes no important immediate hazard and that its provisional authorization may be extended.

- In the meantime, it will examine the available toxicity data concerning the stabilizers employed, with due regard for any problems of synergy.

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF CHLORQUINALDOL AS A PRESERVATIVE

(Opinion delivered on 17 March 1986)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of chlorquinaldol as a preservative, at a maximum concentration of 0.05% in the finished cosmetic product.

CONCLUSION

The Committee cannot give an opinion on the basis of the available information.

BACKGROUND

1. Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 86/199/EEC, authorizes the placing on the market of cosmetic products containing as preservatives only the substances listed in Annex VI to the said Directive, within the limits and at the maximum concentrations laid down therein.

2. The industry has requested that chlorquinaldol be included in the above-mentioned Annex and has submitted a scientific dossier in support of the request.

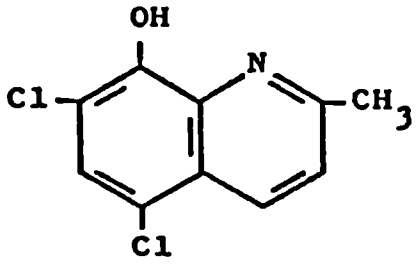
3. The Committee was therefore invited to deliver an opinion on the use of chlorquinaldol as a preservative at a maximum concentration of 0.05% in the finished cosmetic product.

DISCUSSION

4. 5,7-dichloro-2-methylchinolin-8-ol

Synonyms : - Chlorquinaldol

- Sterosan



$C_{10}H_7Cl_2NO$
MW 228.08

5. Practically insoluble in water : moderately soluble in organic solvents (chloroform, acetone, ether).

6. Used as a preservative in cosmetics up to 0.05%. Also used at 3% in ointments and creams in medical and veterinary drugs as antiseptic and fungistatic.

7. Oral LD_{50} values are 2.9 g/kg in rats, 0.583 g/kg in male mice and > 1.0 g/kg in dogs (males and females).
Subcutaneous LD_{50} values are 2.9 g/kg in male mice and 3.1 g/kg in female mice, in rats > 4.0 g/kg, in dogs > 0.5 g/kg. The intraperitoneal LD_{50} values in mice are 0.185 g/kg in males, 0.185 g/kg in females, and in rats 1.39 g/kg.

8. Repeated dermal application of 0.05 ml of a 3% cream to the intact and scarified skin of hairless mice, daily for 28 days, only induced some reddening in 2/10 mice on a few days, while thickening of the skin was seen in 1/10 mice. More severe dermal reactions occurred in 90-day topical application studies in rabbits and dogs.

9. An eye irritation test in rabbits with 0.1 ml cleansing milk containing 0.02, 0.1 or 0.5% did not reveal clearly more eye changes than did the cosmetic without the test compound.

10. The substance is known to possess sensitizing potency for humans. In a study with 5558 patients, 2.4% were positive to a mixture of Vioform + Sterosan. Cross sensitization of Sterosan with other halogenated hydroxyquinolines has been observed.

11. The sub-chronic (90-day) dermal toxicity was examined in rabbits by applying 0.7 g/kg b.w. of an ointment containing 0, 1, 3 or 10% of the test substance each day for 13 weeks (or 0, 7, 21 or 70 mg/kg b.w./day). In the top-dose group all animals died or were killed when moribund in the first 2 weeks. In the top-, and mid-dose group there were haematological changes, and blood was found in urine. Increases in blood urea-N, absence of spermiogenesis, and microscopical renal changes occurred in all treated groups. In this study, oral uptake was not fully excluded, but in a repeat study with the 10% ointment under occlusion similar changes were found though less severe.

12. A 90-day dermal study with the 0, 1, 3 and 10% ointments was also conducted in groups of 2 beagle dogs/sex treated with 7.0 g/dog on 7 days/week. In all treated groups the dogs showed dermal changes at the application sites, enhanced blood sedimentation rate and changes in white blood cell counts. In addition the 3 and 10% groups showed weight loss, increased numbers of leucocytes, increased activity of some blood enzymes and microscopical liver changes.

13. Dermal absorption studies with the ^{14}C-labelled compound in guinea pigs *in vivo* showed that 96-98% of the dose, applied in various formulations, could still be removed from the skin after a 7-hr contact period. In humans treated with a cream, 96% was found not to have penetrated after 8 hrs.

14. In vitro tests with intact skin from guinea pigs and from nude mice showed more penetration (20-30%) especially when the compound was applied in ethanol (40 and 50% respectively into skin of guinea pigs and nude mice).

15. In a study in humans (exposed to Sterosan in ointments and creams), up to 19.5% of a dermal dose was recovered in the urine, while after oral administration of an equal dose (30 mg) the mean urinary excretion (mainly in the form of the glucuronide) was 67.6%.

16. Embryotoxicity studies were conducted in rats and rabbits by dermal application of 0.5, 5.0, 50.0 or 250.0 mg/kg b.w. in a 10% containing ointment under occlusion for 5 hours daily on days 7-16 of pregnancy in rats and on days 7-19 of pregnancy in rabbits.
Apart from local irritation of the skin in the highest dose group of rats and in the two higher dose groups of rabbits, there were no other signs of intolerance. The reproduction data were not influenced by treatment. In the rat study several abnormalities of the skeleton were more frequent in the treatment groups than in controls, but it is stated that the incidences were in the normal range.
The two higher dose groups in the rabbit study showed growth retardation which was attributed to the severe local skin damage. The higher incidence of a few bone abnormalities in the treated groups were not considered to represent embryotoxic or teratogenic effects.

17. An Ames test with up to 100 µg/plate was negative, but 5 µg and above already caused growth depression or complete inhibition of the bacteria. In the mammalian cell culture HGPRT system with Chinese hamster ovary cell line V79 exposed up to 15 µg/ml, no mutagenic activity was detected. The highest concentration tested was distinctly toxic. A micronucleus test in mice given once intraperitoneally 37.5, 75 or 150 mg/kg b.w., with bone marrow counts after 24, 48 and 72 hours did not reveal an increase in micronucleated cells.

18. Information on systemic toxicity is avalable only from dermal studies conducted with small numbers of rabbits and dogs. In rabbits, mortality occurred with 70 mg/kg/day and haematological, hepatic and testicular changes with 21 mg/kg. The no-effect level is probably less than 7 mg/kg b.w. Results of dermal absorption studies vary widely. Of a dermal dose in humans, 19.5% has been recovered in the urine. A no-effect level should be established in a well conducted oral study in a sufficient number of rats.

19. Evaluation is not possible on the basis of the available information.

Information : Colipa dossier, Submission I, October 1985

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF FORMALDEHYDE AND PARAFORMALDEHYDE IN COSMETIC PRODUCTS

(Opinion delivered on 17 March 1986)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of formaldehyde and paraformaldehyde as preservative in cosmetic products under the conditions laid down by Directive 76/768/EEC.

CONCLUSION

The Committee is of the opinion that, at the present time, there is insufficient evidence to change the use of formaldehyde and paraformaldehyde as preservative in cosmetic products under the conditions laid down by the directive 76/768/CEE.

BACKGROUND

1. Article 4 of Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 86/199/EEC, requires Member States to prohibit the marketing of cosmetic products containing preservatives listed in Part I of Annex VI, save within the limits and under the conditions laid down in the Directive.

2. In the case of formaldehyde and paraformaldehyde, these limits and conditions are :

   - Maximum authorized concentration : 0.2% (except for oral hygiene products)
     0.1% (for oral hygiene products)
     concentrations are expressed as free formaldehyde.

   - Limitations and requirements : Prohibited in aerosol dispensers, except for foams

- Conditions of use and warnings which must be printed on the label : Contains formaldehyde (only if the concentration exceeds 0.05%).

3. Under Article 12 of the Directive a Member State may provisionally prohibit the marketing of a cosmetic product in its territory or subject it to special conditions if it can show, on substantiated grounds, that although complying with the requirements of the Directive the product presents a hazard to health. In application of this Article, one Member State has prohibited the use of formaldehyde as an ingredient of cosmetic products, while authorizing the use of starting materials containing formaldehyde as a preservative provided that the concentration of that substance does not exceed 0.2% in the finished product. Under no circumstances, however, may formaldehyde be present in cosmetic products put up in aerosol form (except for foams) or in oral hygiene products. These measures are based on the opinion delivered by a committee of experts appointed by this Member State to study the carcinogenic, mutagenic and teratogenic effects of chemical compounds, which classified formaldehyde among the substances whose carcinogenicity is attested to by experimental but not by epidemiological evidence.

4. The Committee was accordingly requested to deliver an opinion on the use of formaldehyde and paraformaldehyde as preservative in cosmetic products under the conditions set out in paragraphe 2 above.

DISCUSSION

5. Formaldehyde

6. Easily soluble in water.

7. Oral LD_{50} values are 100 - 200 mg/kg in the rat, 260 mg/kg in the guinea pig and $>$ 250 mg/kg in the dog. The dermal LD_{50} in the rabbit (270 mg/kg) is in the range of the oral LD_{50} found in other species, suggesting considerable dermal absorption in rabbits.
8. Formaldehyde is a severe eye irritant in the rabbit. In humans it is a moderate skin irritant and a strong sensitizer. Sensitizing properties may appear at use levels of c. 0.1%. Cases of pulmonary sensitization have been attributed to inhalation exposure of workers.

9. The substance occurs naturally in foods. It is a normal metabolite in humans, and is rapidly oxidized and metabolized via formic acid to carbon dioxide and water. Some amino acids (tryptophan, serine, glycine) are endogenous sources of formaldehyde.

10. Sub-chronic (90-day) administration of 50, 100 or 150 mg/kg b.w. in the drinking water of rats, and of 50, 75 or 100 mg/kg b.w. in the diet of dogs caused growth depression in the top-dose groups, but no gross or microscopic changes.

11. Calves fed skimmed milk with 0.1% formalin (40% formaldehyde w/v) showed severe pathological changes in the stomach. No abnormalities were seen, however, in pigs fed skimmed milk with 0.15 or 0.5% formalin.

12. In a 5-generation study in rats receiving 0.2% calcium formate in their drinking water, no changes were observed in growth rate, or reproduction , nor in gross- or microscopic pathology. Neither were abnormalities seen when hexamethylene tetramine (HMT) was administered in the drinking water over 5 generations of rats at levels of 5 or 50 mg/kg body weight.

13. Treatment of mice with up to 185 mg/kg by gavage on day 6-15 of gestation did not induce signs of embryotoxicity or teratogenicity although the high dose was toxic to the dams.
No teratogenic effects were observed in a dog study by administering 3.1 or 9.4 mg formaldehyde/kg/day or 15 to 31 mg HMT/kg/day during pregnancy.

14. Several long-term oral studies have been conducted in rats or mice. In one mouse study, females showed a slightly increased tumour incidence with 1% HMT or 0.15% formaldehyde in the drinking water. The other oral studies were negative.

15. Two recent initiation-promotion studies in mice, using traditional two-stage skin painting techniques, have been reported. In one study (Krivanek et al., 1983), formaldehyde lacked either initiation or promotor activity after 180 days of observation. In the second study Spangler and Ward (1983) reported that through 48 weeks of observation, formaldehyde showed no activity as an initiator or as a complete carcinogen, but may have had weak promoting activity.

16. Dermal absorption is relatively small. In rats c. 5% of the labelled substance was absorbed from an oil in water cream within 48 hours (Barnik et al. 1985).

17. The inhalation LC_{50} for rats was 250 ppm. In humans, signs of discomfort (irritation of nose and throat, lachrymation) occur when the respirated air contains 4 ppm. Sub-chronic (90-day) exposure of rats to 3.8 ppm in air resulted in interstitial pneumonia. In recent chronic inhalation studies with 2, 6 and 15 ppm in air, squamous cell carcinoma of the nasal cavity were induced in rats and mice. Exposure levels causing nasal tumours also caused pathological changes in the nasal mucosa. No nasal tumours occurred upon chronic inhalation exposure of hamsters to 10 ppm.

18. Formaldehyde induces chromosomal aberrations and DNA damage in several test systems including mammalian cells in culture, and is mutagenic to bacteria, yeasts and the fruit fly, but not to the silkworm, or to mammalian cells in culture. One dominant lethal study in mice was positive, another study was negative.

19. The possible carcinogenicity of formaldehyde in man has been discussed at a recent meeting of a WHO Working Group in Dubrovnik (1985). At least 10 different epidemiological studies were evaluated, of which several indicated an excess of tumours. However, in different studies different sites were involved.
    Moreover, the best designed studies were negative. In one study on more than 1000 deceased embalmers in New York a significant excess of deaths from skin cancer was found (based on 8 cases). Such an effect was not found in a similar study conducted in California (Hopkins 1985). In spite of the great number of studies available, the evidence was considered insufficient to assess the carcinogenic potency of formaldehyde in humans (WHO 1985). This confirms the conclusions drawn by IARC in 1982.

20. Formaldehyde is an irritant and a sensitizer. Repeated oral exposure of rats, mice, and dogs to relatively high levels is well tolerated. The substance possesses mutagenic properties. Carcinogenic properties have been established upon inhalation by rats and mice of relatively low levels, which, however, exerted a cytotoxic effect. There is no evidence to consider formaldehyde a dermal carcinogen, but a long term dermal exposure

study in animals is not available. The substance is on the list of accepted preservatives in cosmetics at levels up to 0.2%. At the present time there is insufficient evidence to change this situation.

21. Information from :

- Data sheet Council of Europe
- Data sheet Nat. Inst. Public Health, the Netherlands
- JECFA 17th Report, WHO Techn. Rep. Series 1974, No. 539
- IARC Monographs 29 (1982) 345-389
- WHO Working group on indoor air quality : radon and formaldehyde. Dubrovnik, 26-30 Aug. 1985. Summary report.
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REPORT OF THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF 8-HYDROXYQUINOLINE AND ITS SULPHATE IN COSMETIC PRODUCTS

(Opinion delivered on 7 January 1986)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of 8-hydroxyquinoline and its sulphate in cosmetic products as a stabilizer for hydrogen peroxide in hair-care preparations at the maximum authorized concentration of 0.3% (calculated as base) in the finished product.

CONCLUSION

The Committee is of the opinion that the use of 8-hydroxyquinoline and its sulphate in cosmetic products as a stabilizer for hydrogen peroxide can be accepted for rinsed off products under the conditions laid down in Directive 76/768/EEC. For non rinsed off products information is requested on skin and eye irritating properties, on dermal absorption and teratogenicity. However, on the basis of the data available, the Committee could accept, for the time being, the use in non rinsed off products under the same conditions.

BACKGROUND

1. Article 4 of Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 85/391/EEC, requires Member States to prohibit the placing on the market of cosmetic products containing substances listed in Part I of Annex III, save within the limits and under the conditions laid down therein.

2. In the case of 8-hydroxyquinoline and its sulphate, these limits and conditions are :

   - Field of application and/or use : As a stabilizer for hydrogen peroxide in rinse-off hair-care preparations.

   - Maximum authorized concentration in the finished product : 0.3% calculated as base

3. The industry has requested that the field of application and/or use be extended to non-rinse-off hair-care preparations.

4. The Committee was accordingly invited to deliver an opinion on the use of 8-hydroxyquinoline and its sulphate as a stabilizer for hydrogen peroxide in hair-care preparations at the maximum authorized concentration of 0.3% (calculated as base) in the finished product.

DISCUSSION

5. Hydroxyquinoline is insoluble in water and ether, slightly soluble in other organic solvents; the sulphate dissolves well in water.

6. Used in cosmetics at dose levels of 0.3% as stabilizer for hydrogen peroxide in hair-care preparations (rinsed off and non rinsed off).

7. LD_{50} values reported are : oral in rats 1.2 g/kg, in guinea pigs $>$ 1.2 g/kg for the free base; i.v. in mice 50 mg/kg, in rabbits 65 mg/kg for the free base; s.c. in mice 25 mg/kg, in rats 200 mg/kg for the sulphate; i.p. in mice 43 mg/kg.

8. Sensitizing properties have been reported from studies in man.

9. Oral administration to dogs resulted in rapid intestinal absorption and renal excretion and slow excretion in the bile.

10. Intravenous treatment of rabbits with a single dose of 8-hydroxyquinoline in amounts of 10 - 50 mg/kg resulted in destruction of the ß-cells in the pancreas and increased blood glucose levels. Pancreatic damage was observed also in several other species upon i.v. administration.

11. Feeding rats 400 mg/kg b.w. for 16 weeks caused hemosiderosis in the liver and spleen. In another rat feeding study hepatotoxicity and renal toxicity occurred on diets providing 100-250 mg/kg b.w. for 30-40 days.

12. In 1977 IARC examined several carcinogenicity studies in mice and rats conducted by oral, subcutaneous and intravaginal administration, and in mice by skin application and bladder implantation. These studies were considered of limited value for various reasons and no evaluation could be made of the

carcinogenicity of this substance. Meanwhile further longterm studies were conducted and reported recently by NTP (1985). Groups of 50 rats/sex and of 50 mice/sex were fed diets containing 0, 1500 and 3000 ppm of the test substance. The top-dose groups showed relatively low body weights. No significant differences in mortality occurred between groups in either species. Extensive gross and microscopic pathology did not reveal treatment-related changes and there was no evidence of carcinogenic properties. Haematological and clinical examinations were not conducted.

13. The substance showed mutagenic properties in the Ames test. A test on induction of aneuploidy in Nuerospora crassa was equivocal. Chromosome aberrations were observed in root tips of Vicia faba, and in bone marrow cells of mice after i.p. injection of 40 mg/kg b.w. Equivocal or inconclusive results were obtained in a variety of other short-term tests such as a Drosophila test, a micronucleus test in mice and a chromosome aberration test in human leucocytes in vitro.

14. No information is available on skin or eye irritation, on dermal toxicity or on dermal absorption. Information on reproductive effects or teratogenicity is also absent. The substance seems to be relatively harmless because 1500 ppm in the diet of rats (75 mg/kg b.w.) and in the diet of mice (150 mg/kg b.w.) was a no effect level. Therefore, the substance can be accepted for rinsed off products. However for non rinsed off products information is requested on skin and eye irritating properties, on dermal absorption and teratogenicity.

Information :
- Data sheet National Institute of Public Health, the Netherlands
- IARC Monograph 13 (1977) 101-112
- NTP Technical Report Series No. 276, April 1985.

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF HEXACHLOROPHENE IN COSMETIC PRODUCTS

(Opinion delivered on 17 March 1986)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of hexachlorophene in cosmetic products under the conditions laid down by Directive 76/768/EEC.

CONCLUSION

In view of the toxic properties and considerable dermal absorption of hexachlorophene, and the possible presence of TCDD, the Committee cannot recommend the use of hexachlorophene in cosmetics.

BACKGROUND

1. Article 4 of Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 86/199/EEC, requires Member States to prohibit the placing on the market of cosmetic products containing preservatives listed in Part I of Annex VI, save within the limits and under the conditions laid down in the Directive.

2. In the case of hexachlorophene, these limits and conditions are :

   - Maximum authorized concentration : 0.1%
   - Limitations and requirements : Prohibited in products for children under three years of age and in intimate hygiene products.
   - Conditions of use and warnings which must be printed on the label : Not to be used for children under three years of age. Contains hexachlorophene.

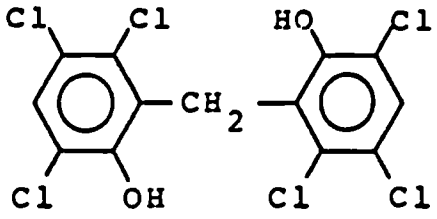
3. Certain Member States would like to discourage or even prohibit the use of hexachlorophene in cosmetic products.

4. The Committee was accordingly invited to deliver an opinion on the use of hexachlorophene in cosmetic products under the conditions laid down in paragraph 2 above.

DISCUSSION

5. 2,2'-Methylenebis[3,4,6-trichlorophenol]

Synonym : Hexachlorophene



$C_{13}H_6Cl_6O_2$

MW 406.92

6. Soluble in ethanol, ether and other organic solvents, practically insoluble in water.

7. Acute effects

Oral LD_{50} values (in mg/kg) are : 66 in male rats, 56 in female rats, 120 in weanling rats, 9 in suckling rats.

A single oral dose of 100 mg/kg may paralyse weanling rats. In children, a single oral dose of 250 mg/kg may be fatal.

A single dermal dose of 600 mg/kg in ethanol may kill rats.

Vigorous washing of pigs with 3% in detergent, once, for 20 minutes, induced hind limb weakness five days later.

Intravenous injection of monkeys, rabbits, dogs and cats with respectively 8.0, 5.0, 10 and 10 mg/kg induced severe pharmacological effects and death.

8. Eye irritation

A test in rabbits with 0.1 ml 2% solution of the monosodium salt in 4% aqueous propylene glycol was negative.

9. Primary skin irritation

Tests with 0.1% and above in acetone were positive in guinea pigs and rabbits, 0.05% and above was positive in 1/10 rabbits. The irritation reaction reached a maximum after 4 days. The irritating potency was less in other vehicles, such as propylene glycol, petrolatum, olive oil, and polyethylene glycol 400. Irritation occurred, however, in each of the vehicles if the concentration was 1.0%. In humans 0.1% in propylene glycol caused irritation, while 10% did not if the vehicle was petrolatum, olive oil, isopropylmyristate, or polyethylene glycol 400 (Morikawa et al. 1974).

10. Phototoxicity tests in rabbits and guinea pigs were positive, inasfar the primary skin irritation reaction caused by 0.1% in acetone was consistently more pronounced on skin sites treated topically and then irradiated with UV, than on skin sites treated topically and not irradiated.

11. Sensitization. A sensitization and a photosensitization test in guinea pigs, which were induced topically with 0.05 ml 2% in acetone, daily for 5 days/week during 2 weeks, and challenged with 0.05 ml 0.001 to 0.1% in acetc was negative (Morikawa et al.1974).

12. Oral short-term

- Rats treated orally with 40 mg/kg/day for 14 days showed paralysis and blood levels of 4 - 6 ppm. When the rats were treated for 42 days with 40 mg/kg/day, 7/30 rats died. Microscopic changes, mainly vacuolization, were observed in the brain and spinal cord. These lesions disappeared slowly (84 days) after treatment. Blood levels were 1 - 8 ppm on day 42.
- Similar effects have been observed in mice, dogs, rabbits and monkeys after repeated oral dosing with 25 - 100 mg/kg.
- Daily oral dosing of rats with 20 mg/kg b.w. for 6 weeks caused spongy vacuolation in the cerebrum and cerebellum (NIPH).
- Rats fed 500 ppm in the diet (25 mg/kg b.w.) showed nervousness and weakness in the hindquarters after 14 days. These clinical signs developed into paralysis within a few weeks after treatment.
- A 90-day rat feeding study with 0, 20, 65 and 200 ppm resulted in vacuolation of the cerebrum and spinal cord in the top-dose group, increased liver weight in the mid-dose group, and no changes in the low-dose group. Blood levels of HCP ranged from 0.5 - 3.0 ppm in the treated groups (NIPH).

13. Dermal short-term

- Rats treated twice daily with 1 ml 3% HCP in detergent or vegetable oil died within 2 - 15 days with symptoms of CNS-damage. Similar signs occurred if the treated sites were washed after 25 minutes (NIPH).
- Young rats (age 0 - 33 days) were immersed (except the head) in 3% HCP for 15 sec. daily, then rinsed with water for 5 sec. and then dried. Clinical signs developed in all rats within 22 days, the younger the rats, the smaller the number of treatments needed. Death occurred in 25% of the treated animals (Delcour-Firquet, 1980).
- Monkeys treated dermally with 0, 5, 20 or 80 mg/kg (as a solution in propylene glycol/ethanol) twice weekly for 3 months developed various signs of intoxication including spongy degeneration of CNS with 80 and 20 mg/kg, while 5 mg/kg was not a clear NEL.
- CNS symptoms developed also in a normal infant after daily treatment for 4 days with 3% HCP in a lotion.

14. Dermal absorption

- In rats, 25 - 55% of a dose of ^{14}C-labelled HCP was found to pass through the intact skin, depending on the vehicle, the sex and the age. Upon rinsing with acetone immediately after application, 13% remained bound to the skin.
- Rat skin is more permeable than skin of guinea pigs or pigs.
- Upon topical application in acetone to the skin of rats and guinea pigs without rinsing 76.6% and 66.9% respectively was recovered in the organs and carcass.
- Dermal absorption is rapid in human babies.
- Many cases of rapid intoxication have been observed upon applying HCP as a desinfectant to burnt skin. In these conditions blood levels varied between 2 and 17 µg/ml (Delcour-Firquet, 1980).
- The use of a 3% HCP solution as a body and hand soap led to blood levels ranging from 0.005 - 0.38 µg/ml. Use of a soap with 0.75% HCP resulted in blood levels from 0.02 - 0.14 µg/ml. Upon use of a mouth wash with 0.5% HCP for 3 weeks blood levels of 0.02 - 0.12 µg/ml were measured.

15. Reproduction

- Feeding rats 0, 20 or 100 ppm in the diet (0, 1 or 5 mg/kg b.w.) for successive generations did not affect the microscopy of the CNS. With 100 ppm, survival of pups was decreased in the F1 generation. No such effect was noticed in F2 generation rats (NIPH).
- In a 3-generation study in rats 50 ppm in the diet did not induce any effect.

16. Teratogenicity

- Rabbits which received orally 0, 3 or 6 mg/kg b.w. on day 6 through 18 of pregnancy did not show an effect on foetal survival. In the top-dose group 2/62 foetuses were grossly abnormal (acrania and ectopic teratosis).
- In another similar study in rats with 6 mg/kg none of the foetuses were structurally abnormal. Apart from delayed ossification, skeletal examination was negative (NIPH).
- Rats treated with 500 ppm in the diet, or with 20 - 30 mg/kg b.w./day by gavage caused some malformations (angulated ribs, cleft palate, micro- and anophthalmia) and reduction in litter size. These dose levels approached those which caused maternal death.
- Pregnant rats treated with a 45% suspension of HCP in the vagina showed maternal toxicity and major malformations in some embryos.
- Subcutaneous injection of mice with 12.5 or 25 mg/kg b.w./day on days 3-8, 7-12 or 11-17 of gestation caused foetal resorptions but no malformations (IARC).
- Babies from hospital personnel who had been exposed to HCP during pregnancy showed an increased incidence of severe and minor malformations (IARC).

17. Metabolism

- Upon oral administration of HCP to rats, 80 - 90% is excreted unchanged in the faeces within 10 days. However, upon i.p. administration, extensive biliary excretion (31-47% of the dose within 24 hours) and enterohepatic circulation occurred. The principal metabolite in bile was the monoglucuronide. Much of the unchanged compound found in the faeces probably resulted from intestinal bacterial hydrolysis of the conjugate (IARC).

- Upon dermal administration to rats c. 70% of total radioactivity was recovered in the faeces, 9% in the urine. In the urine 33-81% of the radioactivity was of the unchanged HCP.
- Dermal application to the monkey resulted in 40% in faeces and 19% in urine. Unchanged HCP in urine was 83-100% of radioactivity in urine.

18. Mutagenicity

- A host-mediated assay in rats fed 100 or 200 ppm in the diet for 90 days showed no reverse mutations in S.typh. G 46.
- No dominant lethal mutations were detected in male mice treated with 2.5 or 5.0 mg/kg b.w. by i.p. injections and subsequently mated with untreated females.
- A chromosomal aberration test with human leucocytes exposed to HCP in vitro at levels of 1-200 mg/l for 6-21 hrs was negative. However, mitosis was suppressed with a concentration as low as 40 mg/l applied for 6 hrs (IARC).

19. Carcinogenicity

- Rats fed 0, 17, 50 or 150 ppm in the diet for 2 years showed no increased incidence of tumours (IARC).
- No indications of carcinogenic properties were observed :
  a) upon feeding 50 ppm in the diet of rats for 2 years;
  b) upon feeding 150 ppm in the diet of C57B mice, or of XVII/G mice for nearly 2 years and 1 1/2 years respectively;
  c) upon administration (route not indicated) of 0.5 mg daily for 20 days to 7 pregnant mice of the XVII/G strain and observing the descendents for 1 1/2 years;
  d) upon s.c. administration to mice of the XVII/G strain of 0.05, 0.05 and 0.1 mg on day 1, 2 and 8 after birth respectively and then observing these mice for their lifetime (Rudalli and Assa 1978).
- Skin painting of mice twice weekly for their lifetime with 0.02 ml acetone containing 1, 5 or 10 mg HCP caused ulceration, necrosis, inflammation of the skin and neurological symptoms. High mortality occurred in the treated groups but there was no increase in incidence of tumours (IARC 1979).

20. HCP is of considerable to high toxicity. The major effect is a degenerative change of the CNS that may occur both upon dermal and oral exposure. Dermal absorption is considerable. Systemic effects upon dermal or oral exposure are the same. Excessive use of skin-care products containing HCP, may result in high blood levels, clinical signs of intoxication, damage to the CNS and death. The no-effect-level was 1 mg/kg b.w. in a 90-day oral toxicity study in rats. In monkeys treated by subcutaneous injection, twice weekly, for 3 months, the NEL was 5 mg/kg. The substance has shown teratogenic properties but no mutagenic or carcinogenic potency. Commercial preparations may contain the extremely toxic TCDD as a contaminant. In view of the toxic properties and considerable dermal absorption of HCP, and the possible presence of TCDD, the use of HCP in cosmetics cannot be recommended.

Information : - Data sheet National Institute of Public Health, the Netherlands (1972) (NIPH)

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- IARC Monographs Vol 20 (1979)
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